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Study of Indicators for Early and Rapid Diagnosis of Radiation Injury Is the Most Important in Patients With Cancer During Radiotherapy

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Abstract

Objective: To establish a complete technical solution for the radiation biological dose estimation, to enable prediction of individuals' response to radiotherapy (RT), and to control treatment dose for reduced irradiation injury and promote repair; and to evaluate the risk of radiation-induced late effects for patients undergoing external photon beam RT and provide the reliable dose–response relationships.

Methods: Select 49 tumor patients using ^{60}Co and linear accelerator for radiation therapy; initial radiation dose was 250 cGy. Chromosome aberration and blood count were analyzed before radiation therapy and 2 hours after the first day of RT.

Results: Two hours after the first day of RT, peripheral blood cell count of lymphocytes of patients with cancer was significantly decreased ($P < .01$). The frequency of chromosome aberration was higher ($P < .01$).

Conclusion: High-dose radiation of the radiation therapy makes significant injuries to peripheral blood lymphocytes.

Keywords
peripheral blood lymphocytes, radiation injuries, first irradiating, dicentric chromosome analysis

Introduction

The International Agency for Research on Cancer reported that almost 21.4 million new cases of cancer will be diagnosed annually, in which about 60% to 70% of patients with cancer receive radiation therapy. Owing to the high mortality of patients with cancer, it covered up the radiation injuries for the cancer patients that caused by radiation therapy.

Radiation oncology, which is a new subject, has a history over centuries. Radiation uses large doses of high-energy beams or particles to destroy cancer cells in a specifically targeted area. Meanwhile, radiation will cause injury to the surrounding normal tissue cells in varying degrees. The side effects and tissue damage not only limit radiation dose escalation but also affect the patient's quality of life. People have paid more attention to the radiation damage of normal tissue while caring about all malignant cells killed. Therefore, it has become an important issue in radiation oncology to seek for measures to decrease local radiation dose and increase antitumor effect. Radiotherapy (RT) doses are physical dose. It cannot truly reflect the level of radiation dose of patient. There is also a need for a potential biological dosimeter, which may be applied for the estimation of biological dose for recent radiation exposure.

Manual scoring of dicentric chromosomes from peripheral blood lymphocytes of individuals exposed to radiation remains as the "gold standard" in biological dosimetry.[1] Hence, there is great interest among cancer researchers in finding ways to protect "innocent" tissues against radiation-induced damage.

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Nowadays, it is an important question to study in the field of treatment for patients with cancer. How to reduce irradiation injury and promote repair has been one of the criticality for improving treatment level of acute radiation therapy. Although the true biological significance of break point regions has not been clear, there is no doubt that research on hot damage point is an important part of study on effect of radiation. A complete technical solution was established about the radiation biological dose estimation, finding a stability and sensitive examination index for biological dose estimation, and throwing controlled treatment dose to reduce irradiation injury and promote repair are worthy of further promotion. Select 49 patients with tumor (including stomach, colon, lung, cervical, and lymphomas cancers) were irradiated by RT using ^{60}Co(15) and linear accelerator (34).[2–4]

With the development of cancer radiation therapy technology, radiobiology, and radiation physics, a lot of biological dosimetry estimation methods were developed. Radiation biodosimetry is an important part of radiation medicine. Some new discoveries and progresses have been made in radiation biodosimetry studies in recent years. Cytogenetic method represented by chromosome aberration analysis as the golden standard of radiation biodosimeter is being transformed to automate analysis, and a number of international, regional, and national laboratory networks of radiation biodosimetry are being established. As a widely acceptable molecular marker of DNA damage, γ-H2AX has made rapid progress in radiation dose estimation. Based on the expressions of protein and genes, further advancements have been made in the studies of metabolites and microRNAs. At the same time, with the development of proteomics technology, there are some breakthroughs in the study of using molecular expression profiling to evaluate radiation dose.

The data on imaging of patient anatomy, RT treatment plan, and types of irradiation source affect the dose that the patient received during RT, but the patient's biomaterial indicators will actually reflect the dose received in the surrounding normal tissue. Evaluating the risk of radiation-induced late effects for patients undergoing external photon beam RT provides the reliable dose–response relationships.

It has become an important issue in radiation oncology to seek for measures to decrease local radiation dose and increase antitumor effect. Researchers have been committed to the research more and more, and this discovery may be used to help to reduce side effects of patients with cancer undergoing RT.

Materials and Methods

Reagents and Instruments

Biochemical RPMI-1640 (Xi'an, China), fetal bovine serum (FBS), and phytohemagglutinin-M were purchased from Invitrogen (GIBCO, Beijing), and potassium chloride and PI were obtained from Sigma Chemicals (Shanghai). Methanol and glacial acetic acid were obtained from Spectrochem (China). Quick CRP analyzer (Shanghai, China); Giemsa stain was purchased from Sigma-Aldrich (St Louis, Missouri), the SANYO MCO-20AIC CO_2 incubator from SANY (Sakata, Japan), and microscope from OLYMPUS (OLYMPUS CK20, Tokyo, Japan).

Blood Samples

Heparinized blood was collected from 49 patients with tumor (including stomach, colon, lung, cervical, and lymphomas cancers) who were irradiated through RT using ^{60}Co(15) and linear accelerator (34). The median age of patients in this trial was 62.95 years (range: 51-72 years; male: 42, female: 7).

This study was cleared by the Gansu Provincial Center for Disease Control and Prevention Ethical Committee and with the informed consent of patients.

Cell Culture and Sample Preparation

The radiation dose was 1.8 to 2.8 Gy/time, treatment of frequency, once a day and five times a week. The first irradiation is 2 hours after the first day of RT.

About 2 mL of the peripheral blood was collected from each patient with tumor before RT and after first irradiation was divided into 0.5 mL portions. Of all, 0.5 mL of the blood was added to 4 mL portion of the culture media (80% RPMI-1640 and 20% FBS). The lymphocytes were cultured in Roswell Park Memorial Institute 1640 culture medium containing FBS, phytoagglutinin, 1% penicillin sodium and 100 mg/mL streptomycin, and 0.04 g/mL colchicines at 37°C in 5% CO_2 in a humidified incubator (Thermo Scientific, Waltham, North Carolina) for 52 hours. Whole blood culture method was adopted, and the proportion of blood and culture medium was 1:10; 0.5 mL heparin lithium was added into 5 mL lymphocyte culture medium as anticoagulant. Cell suspension was prepared. Cells were subjected to hypotonic treatment by 5 mL KCl solution 2 times each 30 minutes and then fixed 4 times with Carnoy solution for 5 minutes each. Slides were produced and subjected for Giemsa staining, air-dried, and coded. It was used to analyze the lymphocyte chromosome aberration.

About 2 mL of the peripheral blood collected was from each patient with tumor before RT and after first irradiating was divided into 0.5 mL portions; 0.5 mL of the blood was added to 4 mL portion of the culture media (80% RPMI-1640 and 20% FBS). The mixture was stimulated with phytohemagg lutinin-M (20 mg/mL) and incubated at 37°C. After 72 hours of incubation, the cells were harvested with a prechilled hypotonic solution (0.075 M) and fixed with a Carboy solution (methanol/acetic acid 5:1). Multiple slides were casted, air-dried, and coded.

Then the slides were stained with 8% Giemsa solution in phosphate buffer (pH 6.8, Propidium Iodine: 1 μg/mL), and scoring was performed blindly manually and with the MetaSystems automatically. In the Giemsa-stained slides, we calculated the frequency of the micronuclei in the binucleated cells with intact cytoplasm using the criteria described in detail by Fenech.[5] Lymphocyte blood counts were measured using Quick CRP analyzer (Hunan, China).

Table 1. The Number of Cells and DICs Analyzed at Each Dose Point in the Fitted "Dose–Effect Curve By DIC Analysis."

Absorbed Dose (Gy)	Cell Number	Dic + r Number	Dic + r/Cell
0	11 000	7	0.000636
0.25	6310	60	0.00951
0.5	3365	115	0.0342
1	2307	222	0.09623
2	1422	422	0.29677
3	1804	1004	0.55654
4	1586	1446	0.91173
5	1130	1560	1.3805

Abbreviation: DIC, dicentric chromosome.

Statistical Methods

The statistical analysis software SPSS version 10.0 was used for the analysis of variance and *t* test for each corresponding groups.

Dicentric Chromosome Analysis and Dose Estimation

All slides were used to analyze the lymphocyte chromosome aberration and micronucleus assay by the Olympus microscope; about 4928 metaphases were analyzed before RT and 4820 metaphases were analyzed after first irradiation.

Accuracy Verification of "Dose–Effect Curve by DIC Analysis"

Our laboratory has established our own calibration curves. Peripheral blood samples were collected from 3 healthy volunteers for analysis of dicentric chromosome (DIC) dose–effect curve. The blood samples were irradiated in International Atomic Energy Agency/World Health Organization Network of Secondary Standard Dosimetry Laboratories, Beijing, China. The irradiation test tubes were used to measure the dose rate by ^{60}Co γ-ray irradiation at 37°C ± 0.5°C water bath. Eight dose points (0, 0.25, 0.5, 1, 2, 3, 4, and 5 Gy) were set for dose–effect curve preparation. The absorbed dose rate was 0.27 Gy/min (Table 1).

Dicentric chromosomes in metaphase cells were analyzed manually. The yield of Dic + r was well fitted by an equation $y = 5.32 \times 10^{-2}D + 4.43 \times 10^{-2} D^2$ (0.27 Gy·min^{-1}; $R^2 = 0.9999$; Table 2).

Results

Peripheral Blood Lymphocyte Chromosome Aberration Analysis

As for structure, the rings and acentric rings increased significantly after first irradiation, which were rarely seen before RT; the frequency of double centromere chromosomes increased; the chromosome conglutination and dissolution appeared.

Dose Estimation: The Fitting of "Dose–Effect Curve by Chromosome Aberration Analysis"

The dose was estimated by dose–effect curve. Increments of chromosome aberration (dic + r) was 291 (Table 3): increments of chromosome aberration (dic + r) = 112 (^{60}Co), and increments of chromosome aberration (dic + r) = 179 (linear accelerator; Table 4).

Based on the frequency of "dic + r" in lymphocytes, values of radiation exposure of the patients with cancer were 0.84 Gy (^{60}Co) and 0.66 Gy (linear accelerator), estimated radiation (^{60}Co) dose < estimated radiation (linear accelerator) dose < true radiation dose (Table 5).

Peripheral Blood Count Comparison Before and After the First Irradiation

By the comparison of the peripheral blood count before and after the first irradiation of 49 patients with cancer, we found that the number of lymphocyte decreased obviously after RT ($P < .01$). About 40% of these patients' peripheral blood lymphocyte decreased to 1000×10^9/L, 30% of them decreased to 900×10^9/L, and 20% of them decreased to 600×10^9/L. Particularly, some of them decreased to 300×10^9/L.

Discussion

The article results showed that the number of peripheral blood lymphocytes decreased sharply; the lymphocyte conversion rate decreased obviously and nontransformed lymphocytes increased significantly. The rings and acentric rings increased significantly after the first irradiation, which were rarely found before RT; the frequency of double centromere chromosomes increased; and the chromosome conglutination and dissolution appeared. Based on the frequency of dic + r in lymphocytes, estimation of radiation exposure of patients with cancer was 0.70 Gy; estimated radiation dose is less than true radiation dose. Based on the frequency of dic + r in lymphocytes, estimation of radiation exposure of the patients with cancer were 0.84 Gy (^{60}Co) and 0.66 Gy (linear accelerator); estimated radiation (^{60}Co) dose < estimated radiation (linear accelerator) dose < true radiation dose.

The decay rate of "dic + r" aberration in vivo has been reported in different literatures, Ramalho and Nascimento[6] proposed that the time for kinetochore distortion to decrease by half was 95 ~ 220 days, with an average of 130 days. Kanda et al[7] followed up the survivors of the accident in Tokaimura, Japan, for 14 months and found that the half-life of dicentric chromosome was 13.5 months. Jin et al[8,9] reported that "dic + r" of "wen" in Jilin accident in 1996 decreased by 12.5% and 24%, respectively, on the 31st and 66 days after being exposed compared to that on the third day after being exposed. The follow-up observation of the patients exposed to the "June 25" accident in Shanghai shows that the decrease in "dic + r" is not obvious 1 month after the exposure, and the number of dicentrics + rings of most patients is obviously decreased 3

Table 2. Chromosome Aberration Analysis Before and After the First Irradiation.[a]

Subject	Number	Average Absorbed Dose (cGy)	Number of Analysis Cell	Chromosome Aberration Distribution					
				r	dic	t	min	ace	Dissolution Phenomena
Before the first irradiation	49	0	4928	0	34 (0.69)	7 (0.14)	5 (0.10)	2 (0.04)	0
After the first irradiation	49	250	4820	58 (1.20)	233 (4.83)	45 (0.93)	19 (0.39)	39 (0.81)	9 (0.21)
P	–	–	–	<.001	<.001	<.001	<.001	<.001	<.001

Abbreviation: ace, acentric fragments of chromosome; dic, dicentric; min, minute; r, centric rings; t, translocation.
[a]The value in bracket is percentage.

Table 3. Analysis of Chromosome Aberration and Estimation of Biological Dosimetry.[a,b]

Subject	Number of Lymphocytes Examined	Increments of Chromosome Aberration (dic + r)		Estimated Radiation Dose (Gy)	True Radiation Dose (Gy)
		"dic + r" Number	Number Per Cell		
After the first irradiating	4820	291	0.060	0.70	2.5

Abbreviation: ace, acentric fragments of chromosome; dic, dicentric; min, minute; r, centric rings; t, translocation.
[a]Based on the frequency of dic + r in lymphocytes, value of radiation exposure of the patients with cancer was 0.70 Gy; estimated radiation dose is less than true radiation dose.
[b]Increments of chromosome aberration (dic + r) = 112 (^{60}Co); increments of chromosome aberration (dic + r) = 179 (linear accelerator).

Table 4. Analysis of Chromosome Aberration and Estimation of Biological Dosimetry.[a]

Subject	Number	Number of Lymphocytes Examined	Dicentric Chromosomes and Rings		Estimated Radiation Dose (Gy)	True Radiation Dose (Gy)
			"dic + r" Number	Number per Cell		
^{60}Co	15	1500	112	0.075	0.84	2.5
Linear accelerator	34	3320	179	0.054	0.66	2.5

Abbreviation: ace, acentric fragments of chromosome; dic, dicentric; min, minute; r, centric rings; t, translocation.
[a]Based on the frequency of "dic + r" in lymphocytes, values of radiation exposure of the patients with cancer were 0.84 Gy (^{60}Co) and 0.66 Gy (linear accelerator); estimated radiation (^{60}Co) dose < estimated radiation (linear accelerator) dose < true radiation dose.

Table 5. The Peripheral Blood Count Comparison Before and After the First Irradiation of Patients With Cancer.

Subject	Number	WBC ($\times 10^9$/L)	RBC ($\times 10^{12}$/L)	PLT ($\times 10^9$/L)	HB (g/L)	Lymphocyte ($\times 10^9$/L)	Neutrophil ($\times 10^9$/L)
Before the first irradiation	49	7.935 ± 3.720	4.895 ± 1.820	158.0 ± 57.2	133 ± 22.0	2.179 ± 0.786	4.634 ± 3.225
After the first irradiation	49	6.788 ± 2.460	4.203 ± 0.849	140.7 ± 51.5	127 ± 18.6	1.149 ± 0.596	4.829 ± 2.453

Abbreviations: HB, hemoglobin; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

months after the exposure. Previous studies believed that for the estimation of the biological dose of dic + r in the acute and whole-body irradiation, blood should be taken as soon as possible after the accident, preferably within 48 hours and no later than 60 days.[10] The cumulative exposure dose estimation based on stable aberration is slightly higher than dic + r.[11]

This study shows that local inhomogeneous acute exposure can be induced by RT. Because most of the radiation is used to kill tumor cells, only a small portion of normal tissue around the tumor is exposed to a small amount of radiation. The total body equivalent dose given by chromosomal aberration analysis was more consistent with the actual exposure. It's not RT dose, it had more clinical guiding significance.

Lymphocyte, which is a kind of important immunologic substances in human body, was seriously injured by irradiating no matter in quantity or hereditary material in the initial stage of the RT. As an indicator which was used to test the justification of the RT dose, the reasonable number of peripheral blood lymphocyte should not be less than 0.9×10^9/L. The analyses of peripheral blood lymphocyte chromosome aberration were used to estimate the biological dose and guide the RT to work better. Changes in the number of peripheral blood lymphocytes, white blood cells,

and platelets as well as the degree of bone marrow cell proliferation are the main hematological indicators to judge the severity of acute radiation injury.[12] In the "4.26" ^{60}Co source radiation accident in Henan province, the test results of hematological indicators of the exposed personnel were significantly correlated with the exposed dose.[13] This is consistent with reports by de Jager et al.[14]

Most of the patients with lung cancer were treated with RT which can lead to radiation-induced lung injury, the skin was burnt by radiation. Radiotherapy for cases with nasopharyngeal carcinoma can lead to brain damage; vascular injury is one of the most common effects of RT on normal tissues. All these data, including long-term genitourinary side effects, were presented at the 48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology in Philadelphia. For example, this study was designed to evaluate the integral dose (ID) received by normal tissue from intensity-modulated radiotherapy (IMRT) for prostate cancer. Twenty-five radiation treatment plans including IMRT using a conventional linac with both 6 MV (6MV-IMRT) and 20 MV (20MV-IMRT), as well as 3-dimensional conformal radiotherapy (3DCRT) using 6 MV (6MV-3DCRT) and 20 MV (20MV-3DCRT) and IMRT using tomotherapy (6MV; Tomo-IMRT) were created for 5 patients with localized prostate cancer. The ID (mean dose $\times$ tissue volume) received by normal tissue (NTID) was calculated from dose–volume histograms. The 6MV-IMRT resulted in 5.0% lower NTID than 6MV-3DCRT; 20 MV beam plans resulted in 7.7% to 11.2% lower NTID than 6MV-3DCRT. Tomo-IMRT NTID was comparable to 6MV-IMRT. Compared to 6MV-3DCRT, 6MV-IMRT reduced IDs to the rectal wall and penile bulb by 6.1% and 2.7%, respectively. Tomo-IMRT further reduced these IDs by 11.9% and 16.5%, respectively. The 20 MV did not reduce IDs to those structures. The difference in NTID between 3DCRT and IMRT is small. The 20 MV plans somewhat reduced NTID compared to 6 MV plans. The advantage of tomotherapy over conventional IMRT and 3DCRT for localized prostate cancer was demonstrated in regard to dose sparing of rectal wall and penile bulb while slightly decreasing NTID as compared to 6MV-3DCRT.[15] "The relation between the dosimetric factors and side effects was also analyzed with receiver operating characteristic curves.[16]

The occurrence of the distal effect of radiation damage in hematopoietic system is closely related to the exposure dose, the radiosensitivity of hematopoietic parenchyma and mesenchyme, the rate of damage repair, and the probability of gene mutation, including anemia, leukemia, myelodysplastic syndrome, and so on. Through the study on the exposed persons of Hiroshima atomic bomb explosion in Japan and the cleanup personnel of chernobyl nuclear explosion accident, it was found that the incidence of leukemia increased with the increase in the exposure dose, among which the top 3 incidence rates were acute lymphocytic leukemia, acute myeloid leukemia, and chronic myelogenous leukemia.[17]

Conclusions

High-dose radiation of the radiation therapy has significant injuries to peripheral blood lymphocytes. In summary, the results from the present study indicate that chromosome aberration analysis provides a reliable estimate for biological exposure to radiation, which is shown to have a critical role in estimating the radiation dose. This may enable faster and more reliable estimation of radiation exposure, leading to better treatment for patients with cancer.

Establishing a complete technical solution for the radiation biological dose estimation, finding a stable and sensitive examination index for biological dose estimation, and controlling treatment dose to reduce irradiation injury and promote repair are worthy of further promotion.

For the time being, the study on medical radiation protection is not only focused on the occupational workers and patients but on the accompanied new RT technology. The discovery may one day be used to help reduce side effects in patients with cancer undergoing RT. Evaluating the risk of radiation-induced late effects for patients undergoing external photon beam RT provides the reliable dose–response relationships.

Authors' Note

Gang Liu and Li-Mei Niu analyzed the data statistically. All authors have read and approved the final manuscript.

Declaration of Conflicting Interests

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